REMARKS

Status of the Claims

Claims 13-32 are currently pending in the application. Claims 1-13 and 23-26 stand rejected. Claims 14-22 and 27 are withdrawn as being drawn to a non-elected invention. Claims 13 and 21-27 have been amended as set forth herein. Claims 1-12 have been cancelled herein. All amendments and cancellations are made without prejudice or disclaimer. New claims 28-32 have been added herein. No new matter has been added by way of the present amendments. Specifically, the amendment to claim 13, and new claims 28-32 are supported by the specification at, for instance, Table 2, specifically corresponding to h5H-m02, h5H-m07 and h5H-m09 of Table 2. Claims 22, 23 and 27 have been amended herein to change their dependency from cancelled claim 1 to new claim 28. Claims 21 and 24-26 have also been amended to change their dependency and to direct the claims to the elected subject matter. Reconsideration is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-13 and 23-26 stand rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*See*, Office Action of February 7, 2007, at page 3, hereinafter, "Office Action"). Claims 1-12 have been cancelled herein without prejudice or disclaimer, thus obviating the rejection as to these claims. Applicants traverse the rejection as to the remaining claims as set forth herein.

The Examiner states that the phrase "a polypeptide constituting each region contained in the single-chain polypeptide" in claim 13 is indefinite. (*Id.*). The Examiner states that it is unclear if Applicants intended to use the term "CDRs" instead of the language recited. The Examiner also states the phrase, "two kinds of a single-chain polypeptide" in claim 13 is unclear. (*Id.*).

Although Applicants do not agree that claim 13 is indefinite, to expedite prosecution, claim 13 has been amended herein without prejudice or disclaimer to not recite the phrases forming the basis of the present rejection.

Therefore, reconsideration and withdrawal of the indefiniteness rejection of claim 13 are respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 9 and 10 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. (*See*, Office Action, at page 3). Claims 9 and 10 have been cancelled herein without prejudice or disclaimer thus obviating the rejection of these claims.

Enablement

Claims 9, 10 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. (*See*, Office Action, at page 5). Claims 9, 10 and 12

have been cancelled herein without prejudice or disclaimer thus obviating the rejection of these claims.

Rejections Under 35 U.S.C. § 102(b)

Deo, U.S. Patent No. 5,922,845

Claims 1-3, 5-8, 13 and 23-26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Deo, U.S. Patent No. 5,922,845 (hereinafter referred to as "Deo"). (*See*, Office Action, at page 8). Claims 1-3 and 5-8 have been cancelled herein without prejudice or disclaimer, thus obviating the rejection as to these claims. Applicants traverse the rejection as to the remaining claims as set forth herein.

The Examiner states that Deo discloses diabody-type bispecific antibodies as recited in the claims. (*Id.* at page 10).

The bispecific antibody of Deo is prepared by a chemical reaction of two "Fab" polypeptides from two monoclonal antibodies, as described lines 34-64 in column 25 of Deo. The specificities of these Fab are clearly different from those of the humanized diabody-type bispecific antibody of amended claim 13 of the present invention, from which claims 23-26 also depend.

That is, a single-chain polypeptide of the amended claim 13 constitutes a humanized diabody-type bispecific antibody with specific sequences and has a completely different structure from scFv, which contains heavy-chain and light-chain variable regions of the same parent antibody, as disclosed in Kipriyanov, or from V_H and V_L sequences as disclosed in Clackson.

It is now also clear that the humanized diabody-type bispecific antibody of claim 13 (and new claim 28) of the present invention is not a bispecific $F(ab')_2$ fragment as disclosed in Carter and Negri. Thus, the reference cited by the Examiner does not anticipate or even suggest the humanized diabody-type bispecific antibody specifically defined in claim 13, new claim 28, and claims 23-26, and new claims 29-32.

Furthermore, it is noted that none of these cited references disclose all of the SEQ ID NOS presently recited in claim 13 and new claim 28, and also therefore in the claims that depend therefrom which incorporate all of the limitations of claims 13 and 28. Thus, Dco cannot anticipate the presently claimed invention. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (*See, Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)).

Reconsideration and withdrawal of the anticipation rejection of claims 13 and 23-26 are respectfully requested.

Kipriyanov et al.

Claims 13 and 23-26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Kipriyanov et al., *Protein Engineering*, 10(4):445-453, 1997 (hereinafter referred to as "Kipriyanov et al."). (*See*, Office Action. at page 10). Applicants traverse the rejection as set forth herein.

The Examiner states that claim 13 appears to encompass a single chain Fv antibody which binds to an antigen present on cytotoxic or phagocytic cells. (*Id.* at pages 10-11).

Kipriyanov et al., according to the Examiner, discloses an scFv in PBS which comprises heavy and light chain variable regions of the OKT3 antibody, which binds to CD3. (*Id.* at page 11).

However, as commented upon, above, with respect to the anticipation rejection over Deo, Applicants believe that claim 13, as amended, and indirectly, claims 23-26, are not anticipated by Kipriyanov et al. That is, a single-chain polypeptide of the amended claim 13 constitutes the humanized diabody-type bispecific antibody and has a completely different structure from scFv, which contains heavy-chain and light-chain variable regions of the same parent antibody, as disclosed in Kipriyanov et al. Since Kipriyanov et al. do not disclose all of the limitations of the presently claimed invention, Kipriyanov et al. cannot anticipate the presently claimed invention. (*See, Verdegaal Bros*, 814 F.2d at 631, 2 U.S.P.Q.2d at 1053).

Therefore, reconsideration and withdrawal of the anticipation rejection of claims 13 and 23-26 are respectfully requested.

Carter, U.S. Patent No. 6,407,213

Claims 1, 3-8, 12 and 23-26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Carter, U.S. Patent No. 6,407,213 (hereinafter referred to as "Carter"). (*See*, Office Action, at page 12). Claims 1, 3-8 and 12 have been cancelled herein without prejudice or disclaimer, thus obviating the rejection as to these claims. Applicants traverse the rejection as to the remaining claims as set forth herein.

The Examiner states that Carter discloses a humanized bispecific $F(ab')_2$ antibody fragment wherein one of the Fab' arms binds to CD3 and the other binds to $p185^{HER2}$. (*Id.*). However, as already discussed, above, with respect to the Kipriyanov et al. and Deo references,

the humanized diabody-type bispecific antibody of claim 13 of the present invention is not a bispecific $F(ab')_2$ fragment as disclosed in Carter. Carter does not disclose all of the limitations of the presently claimed invention, as recited in claim 13 and new claim 28, especially all of the SEQ ID NO sequences recited. Thus, Carter cannot anticipate the presently amended claims. (*See, Verdegaal Bros.*, 814 F.2d at 631, 2 U.S.P.Q.2d at 1053).

Thus, reconsideration and withdrawal of the anticipation rejection of claims 23-26 are respectfully requested.

Clackson et al.

Claim 13 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Clackson et al., *Nature*, 352:624-628, 1991 (hereinafter referred to as "Clackson et al."). (*See*, Office Action, at page 13). Applicants traverse the rejection as set forth herein.

The Examiner states that Clackson et al. disclose V_H and V_k sequences wherein the sequences comprise CDR regions identical to those found in SEQ ID NO:44. (*Id.*). However, a single-chain polypeptide of the amended claim 13 constitutes a humanized diabody-type bispecific antibody and has a completely different structure from scFv, which contains heavy-chain and light-chain variable regions of the same parent antibody, as disclosed in Kipriyanov, or from V_H and V_k sequences as disclosed in Clackson. Thus, Clackson et al. do not disclose all of the limitations of the presently claimed invention, as recited in amended claim 13 and new claim 28, especially all of the SEQ ID NO sequences recited in the claims. Thus, Clackson et al. cannot anticipate the presently amended claims. (*See*, *Verdegaal Bros*, 814 F.2d at 631, 2 U.S.P.Q.2d at 1053).

Reconsideration and withdrawal of the anticipation rejection of claim 13 are respectfully requested.

Abstract #2125 or Abstract #3P-214

Claims 1-13 and 23-26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Abstract # 2125, 75th Annual Congress of The Japanese Biochemical Society, 74(8), August 25, 2002 (hereinafter referred to as "Abstract #2125") or Abstract #3P-214, 61st Annual Meeting of the Japanese Cancer Association, August 20, 2002 (hereinafter, "Abstract #3P-214"). (*See*, Office Action, at page 14). Claims 1-12 have been cancelled herein without prejudice or disclaimer, thus obviating the rejection as to these claims. Applicants traverse the rejection as to the remaining claims as set forth herein.

The Examiner states that the Abstracts, as translated by Applicants, disclose a process for producing bispecific antibodies which comprise binding sites from the OKT3 and 528 antibodies. (*Id.*). However, neither of the abstracts cited disclose all of the limitations recited in amended claim 13 and new claim 28. Thus, the abstracts cannot anticipate the presently claimed invention. (*See*, *Verdegaal Bros*, 814 F.2d at 631, 2 U.S.P.Q.2d at 1053).

Reconsideration and withdrawal of the anticipation rejection of claims 13 and 23-26 are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-8, 12 and 23-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Renard et al., *Am. J. Path.*, 160(1):113-122, 2002 (hereinafter, "Renard et al.") in view of

Krebber et al., *J. Immunological Methods*, 201:35-55, 1997 (hereinafter, "Krebber et al.") and further in view of Gussow et al., *Methods in Enzymology*, 203:99-121, 1991 (hereinafter, "Gussow et al."). (*See*, Office Action, at page 15). Claims 1-8 and 12 have been cancelled herein without prejudice or disclaimer, thus obviating the rejection as to these claims. Applicants traverse the rejection as to the remaining claims as hereinafter set forth.

The Examiner states that Renard et al. disclose or suggest an anti-CD3/anti-EGFR bispecific antibody and that this antibody may be used in methods of tumor therapy and that this therapy would be more effective if the bispecific antibody were expressed as a single-chain bispecific antibody, etc. (*Id.* at pages 15-16). The Examiner also states that Krebber et al. disclose or suggest methods of cloning functional antibody variable domains to make scFvs. (*Id.* at page 16). The Examiner further states that Gussow et al. disclose or suggest methods for humanizing such antibodies. (*Id.*). The Examiner thus concludes that it would have been *prima facie* obvious to combine these three references to make humanized, bispecific diabody-type antibodies comprising an anti-CD3 binding site and an anti-EGFR binding site. (*Id.*).

However, the bispecific antibody disclosed or suggested in Renard et al. is secreted by a hybrid-hybridoma produced by somatic fusion of the hybridomas producing monoclonal antibody MINT5 and monoclonal antibody 298.1, respectively. Thus, the humanized diabody-type bispecific antibody recited in claim 13, and new claim 28, is entirely different in sequence from the antibodies disclosed in the cited reference.

Nowhere in the cited references is it suggested or disclosed to use the specific sequences recited by amended claim 13, and by dependency, claims 23-26. Thus, since the cited references fail to disclose or suggest all of the limitations of the presently pending claims, the references,

even considered in combination, cannot properly form the basis of a *prima facie* case of obviousness. (*See, In re Vaeck*, 947 F.2d 488 at 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)).

Furthermore, it appears that Renard et al simply refer to newly developed technologies such as bispecific diabodies and humanized antibodies without actually providing examples. Whereas the scFv disclosed in Krebber et al. do not correspond to the single-chain polypeptide that constitutes the diabody-type bispecific antibody. Thus, even upon combination of the constructs of these two cited references, the outcome would either not be operable or not work as the presently claimed invention does.

Thus, one of ordinary skill in the art would not be motivated to modify the bispecific antibody of Renard et al. to produce the present humanized diabody-type bispecific antibody based on the disclosures of Krebber et al. and Gussow et al.

Reconsideration and withdrawal of the obviousness rejection of claims 23-26 are respectfully requested.

CONCLUSION

If the Examiner has any questions or comments, please contact Thomas J. Siepmann, Ph.D., Registration No 57,374, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

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